(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 May 2003 (01.05.2003)

PCT

(10) International Publication Number
WO 03/035068 A1

(51) International Patent Classification[7]: A61K 31/436, 31/133, 31/135

(21) International Application Number: PCT/EP02/11799

(22) International Filing Date: 22 October 2002 (22.10.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0125443.2 23 October 2001 (23.10.2001) GB
0127341.6 14 November 2001 (14.11.2001) GB

(71) Applicant *(for all designated States except AT, US)*: NOVARTIS AG [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: NOVARTIS PHARMA GMBH [AT/AT]; Brunner Strasse 59, A-1235 Vienna (AT).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: MEINGASSNER, Josef, Gottfried [AT/AT]; Max Margules Weg 10, A-2380 Perchtoldsdorf (AT).

(74) Agent: GROS, Florent; NOVARTIS AG, Corporate Intellectual Property, Patent & Trademark Department, 4002 Basel (CH).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/035068 A1

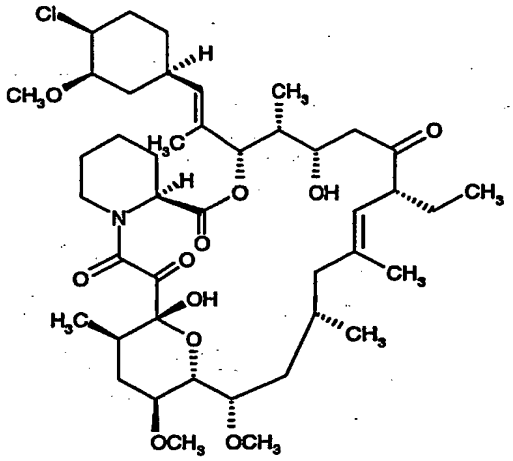
(54) Title: MACROLIDES CONTAINING PHARMACEUTICAL COMPOSITIONS

(57) Abstract: A pharmaceutical compound comprising a compound of formula I and a pharmaceutically acceptable 2-amino-1,3-propanediol beside one or more pharmaceutically acceptable excipient(s).

MACROLIDES CONTAINING PHARMACEUTICAL COMPOSITIONS

The present invention relates to pharmaceutical compositions, e.g. for the treatment of pathological conditions comprising co-administration of pharmaceutically active agents. Treatment includes prevention and/or therapy.

In one aspect the present invention provides a pharmaceutically active compound of formula



I

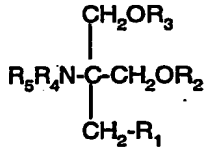
such as disclosed in EP 427 680 (33-epi-33-chloro-FR 520 of example 66a), and a 2-amino-1,3-propanediol beside one or more pharmaceutically acceptable excipient(s).

Pharmaceutically acceptable excipient(s) e.g. includes pharmaceutically acceptable auxiliaries, carrier(s), diluent(s). A 2-amino-1,3-propanediol may comprise one or more 2-amino-1,3-propanediols.

A compound of formulal I, is known to be active for the treatment of various disorders/diseases such as e.g. inflammatory conditions, immunologically-mediated disorders, or autoimmune diseases, e.g. vasculitides, glomerulonephritides, atopic dermatitis,allergies (such as allergic contact eczema, asthma), psoriasis, systemic lupus erythematodes, rheumatoid arthritis, inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), multiple sclerosis, insulin-dependent diabetes, Sjögren's syndrome, endogenous posterior uveitides (in particular Behcet`s disease), Hashimoto`s thyroititis and

to prevent rejections of xenografts or allografts, e.g. including heart, renal, hepatic or bone marrow transplants; graft vessel diseases or graft vs host diseases.

A 2-amino-1,3-propanediol as referred to herein includes a compound of formula



II

wherein

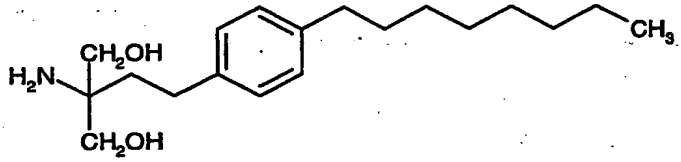
R_1 is an optionally substituted straight- or branched (C_{12-22})carbon chain, e.g. an alkyl chain, which is optionally interrupted by optionally substituted phenylene, and, independently of each other, R_2, R_3, R_4 and R_5 are H or lower alky. When the carbon chain in the meaning of R_1 is substituted, it is preferably substituted by halogen, nitro, amino, hydroxy or carboxy. When the carbon chain is interrupted by optionally substituted phenyl, the carbon chain is preferably unsubstituted. When the phenylene moiety is substituted, it is preferably substituted by halogen, nitro, amino, methoxy, hydroxy or carboxy. "Lower alkyl" includes (C_{1-4})alkyl. Such compounds are e.g. disclosed in EP627406, EP778263, EP1002792 or WO02/06268, the relevant disclosure of which, in particular with respect to the compounds, is incorporated herein by reference.

Preferred compounds include compounds of formula II, wherein R_1 is a straight or branched, preferably straight, (C_{13-20})carbon chain optionally substituted by nitro, halogen, amino, hydroxy or carboxy, and, more preferably compounds of formula II, wherein R_1 is phenylalkyl, optionally substituted by halogen, e.g. wherein alkyl is (C_{1-6})alkyl, optionally substituted by hydroxy, and wherein phenyl is substituted by straight or branched (C_{6-14})alkyl and optionally by halogen. More preferably, R_1 is phenyl(C_{1-6})alkyl, wherein the phenyl group is substituted by straight or branched, preferably straight, (C_{6-14})alkyl, such as (C_{6-14})alkyl-phenyl-(C_{1-6})alkyl. If R_1 is phenylalkyl, wherein phenyl is substituted by straight or branched (C_{6-14})alkyl,the phenyl group may be substituted by alkyl in ortho, meta or para position, preferably in para position. Preferably each of R_2 to R_5 is H.

A pharmaceutical composition may comprise a compound of formula I and a 2-amino-propanol, e.g. one as described in EP 778263, beside one or more pharmaceutically acceptable excipient(s).

In another preferred embodiment a 2-amino-1,3,-propanediol or a 2-amino-propanol is a compound having lymphocyte homing properties. Such properties may be identified according to a test like e.g. the following: A compound to be tested or the vehicle is administered orally by gavage to rats. Tail blood for hematological monitoring is obtained on day 11 to give the baseline individual values, and at 2, 6, 24, 48 and 72 hours after application. A lymphocyte homing agent is a compound which depletes peripheral blood lymphocytes by more than 50% six hours, e.g. after administration of a dose smaller than 5 mg/kg, preferably smaller than 3 mg/kg.

A still more preferred compound of a compound of formula II is a compound of formula



IIa

e.g. 2-amino-2[2-(4-octylphenyl)ethyl]propane-1,3-diol hydrochloride. A 2-amino-1,3-propanediol, e.g. a compound of formula II, may be useful, on the basis of observed activity, e.g. as described in EP 627406, as immunomodulators, e.g. immunosuppressants, e.g. in the treatment of allograft rejections. E.g. as described in WO 98/22100, 2-amino-1,3-propanediols, e.g. of formula II, may inhibit graft vessel disease and are particularly indicated to prevent or treat chronic rejection in a transplanted organ, and additionally may suppress xenograft rejection.

According to the present invention a 2-amino-1,3-propanediol or a 2-amino-propanol is pharmaceutically active and pharmaceutically acceptable.

A compound of formula I and a 2-amino-1,3-propanediol include compounds in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate, where such forms exist. The compounds according to the present invention

- in free form may be converted into a corresponding compound in the form of a salt;
- in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in unsolvated form;

and vice versa.

The pharmaceutical activity of a compound in free form is in a similar range as that of a compound in salt/solvate form. A solvate includes a hydrate. A salt includes a pharmaceutically acceptable salt.

E.g. pharmaceutically acceptable salts of a compound of formula II include salts of a compound of formula II with an acid, e.g. including an inorganic acid, such as hydrochloric acid, hydrobromic acid and sulphuric acid, and including an organic acid, such as acetic acid, fumaric acid, maleic acid, benzoic acid, citric acid, malic acid, methanesulfonic acid and benzenesulfonic acid, and, if a carboxy group is present, salts with

- metals such as sodium, potassium, calcium and aluminium,
- amines, such as triethylamine, and
- dibasic amino acids, such as lysine.

In a preferred embodiment the compounds of formula II or those as described in EP1002792 includes phosphates of said compounds.

A compound of formula I and a compound of formula II may exist in isomeric forms and the present invention includes a compound of formula I and a 2-amino-1,3-propanediol according to the present invention in any isomeric form and any isomeric mixture. E.g. if a compound of formula I and a 2-amino-1,3-propanediol according to the present invention has one or more asymmetric centers in the molecule, the present invention includes the compound in the form of various optical isomers, as well as racemates, diastereoisomers and mixtures thereof.

We have now surprisingly found, that in an animal model of experimental autoimmune uveititis (EAU) wherein a compound of formula I or a 2-amino-1,3-propanediol show pharmaceutical activity, an increased activity is achieved when the compound of formula I and the 2-amino-1,3-propanediol, e.g. a compound of formula II, are co-administered in e.g. suboptimal doses. That increased activity of the co-administered compounds is remarkable higher than that of each single compound tested at the e.g. suboptimal dose level.

The same principle is believed to be valid for all diseases wherein either a compound of formula I or a 2-amino-1,3-propanediol shows pharmaceutical activity, e.g. including inflammatory conditions, immunologically-mediated disorders, or autoimmune diseases, e.g. vasculitides, glomerulonephritides, atopic dermatitis,allergies (such as allergic contact eczema, asthma), psoriasis, systemic lupus erythematodes, rheumatoid arthritis, inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), multiple sclerosis,

insulin-dependent diabetes, Sjögren's syndrome, endogenous posterior uveitides (in particular Behcet`s disease), Hashimoto`s thyroititis and to prevent rejections of xenografts or allografts, e.g. including heart, renal, hepatic or bone marrow transplants; graft vessel diseases or graft vs host diseases.

In another aspect the present invention provides a package comprising a compound of formula I in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s) and comprising instructions for simultaneous or sequential administration of a 2-amino-1,3-propanediol.

In another aspect the present invention provides a package comprising a 2-amino-1,3-propanediol in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s) and comprising instructions for simultaneous or sequential administration of a compound of formula I.

In another aspect the present invention provides a pharmaceutical kit, e.g. a package, comprising a compound of formula I in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s), and a 2-amino-1,3-propanediol in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s) in the same package.

In another aspect the present invention provides a method of improving the pharmaceutically activity of a compound of formula I as described earlier which method comprises co-administrating a compound of formula I and a 2-amino-1,3-propanediol to a subject in need of a treatment with a compound of formula I and/or with a 2-amino-1,3-propanediol.

The compound of formula I and a 2-amino-1,3-propanediol may be co-administrated in different ways:

a) In the form of fixed combinations, comprising a compound of formula I and a pharmaceutically active 2-amino-1,3-propanediol in the same pharmaceutical composition;

b) In the form of a (pharmaceutical) kit, in which a compound of formula I and a 2-amino-1,3-propanediol are present in the form of separate pharmaceutical compositions, sold in the same package, e.g. with instruction for co-administration;

c) in the form of free combinations, in which a compound of formula I and a 2-amino-1,3-propanediol are packaged separately, e.g. in the form of pharmaceutical compositions, wherein each of the packages include instructions for simultaneous or sequential administration.

The most efficient ratio of a compound of formula I and a 2-amino-1,3-propanediol may be dependent e.g. on the indication to be treated. Appropriate dosages and dosage ranges will of course vary depending upon, for example, the active compounds of the present invention used, the host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range of that which is known for a macrolactam like a pharmaceutically active compound of formula I and a pharmaceutically active 2-amino-1,3-propanediol, e.g. below these optimal dosages, administered, for example, in divided doses, e.g. up to four times a day. In general, satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.5 mg/kg to about 15 mg/kg, preferably 1 mg/kg to about 15 mg/kg animal/human body weight of a compound of formula I and form about 0.005 mg/kg to 0.1 mg/kg, prfereably 0.01 mg/kg to 0.1 mg/kg of a compound of formula II. Preferred ratios of compound I to II are in a range between about 3000 to 10, preferably 500 to 10.

The active compounds of the present invention may be administered by any conventional route, e.g. systemically, for example orally, e.g. in form of tablets or capsules, or parenterally, e.g. in the form of injectable solutions or suspensions; and topically, such as epicutaneous, intranasal, intratracheal administration.

In another aspect the present invention provides a method of treatment of diseases, wherein a compound of formula I and/or a 2-amino-1,3-propanediol are pharmaceutically active, e.g. including inflammatory conditions, immunologically-mediated disorders, or autoimmune diseases, e.g. vasculitides, glomerulonephritides, atopic dermatitis,allergies (such as allergic contact eczema, asthma), psoriasis, systemic lupus erythematodes, rheumatoid arthritis, inflammatory bowel diseases (e.g. Crohn's disease, ulcerative colitis), multiple sclerosis, insulin-dependent diabetes, Sjögren's syndrome, endogenous posterior uveitides (in particular Behcet`s disease), Hashimoto`s thyroititis and to prevent rejections of xenografts or allografts, e.g. including heart, renal, hepatic or bone marrow transplants;

graft vessel dieseases or graft vs host diseases, comprising administering to a subject in need of such treatment an effective amount of a compound of formula I and a 2-amino-1,3-propanediol; e.g. in the form of

- a fixed combination, e.g. in the form of a pharmaceutical composition,
- a kit, e.g. in the form of a pharmaceutical composition of a compound of formula I and a pharmaceutical composition of a 2-amino-1,3-propanediol in the same package,
- a package comprising a compound of formula I or a 2-amino-1,3-propanediol, e.g. in the form of pharmaceutical compositions, and comprising instructions for simultaneous or sequential co-administration.

In a preferred embodiment of the present invention a compound of formula I is co-administered with a compound of formula IIa.

The compound of formula I and a 2-amino-1,3-propanediol may be administered as the sole ingredients or together with other drugs in immunomodulating regimens or other anti-inflammatory agents. For example the compounds may be used in combinations with cyclosporins, rapamycins or other ascomycins, or their immunosuppressive analogs, e.g. cyclosporin A, cyclosporin G, FK-506, rapamycin, 40-O-(2-hydroxy)ethyl-rapamycin, etc.; corticosteroids; cyclophosphamide; azathioprene; methotrexate; brequinar; leflunomide; mizoribine; mycophenolic acid; mycophenolate mofetil; 15-deoxyspergualine; immunosuppressive monoclonal antibodies, e.g. monoclonal antibodies to leukocyte receptors, e.g. to MHC, CD2, CD3, CD4, CD7, CD25, CD28, B7, CD40, CD45 or CD58 or to their ligands; or other immunomodulatory compounds, e.g. CTLA4-Ig.

Tests for the determination of the activity of a compound of formula I and 2-amino-1,3-propanediols are known. A model of experimental autoimmune uveitits (EAU) as described e.g. in *Clin. Immunol. Immunopathol. 1986; 39: 329 – 336, McAllister et al.(1986)* can be used.

In another aspect the present invention provides the use of a compound of formula I together with a 2-amino-1,3-propanediol, e.g. administered either simultanously or sequentially, as a pharmaceutical; and
the use of a combination of a compound of formula I and a 2-amino-1,3-propanediol in the preparation of a medicament for the treatment of diseases, wherein the compound of

formula I or a 2-amino-1,3-propanediol are pharmaceutically active. Treatment includes prevention and/or therapy.

Description of the Figures

In **Figure 1**, results of the Experimental autoimmune uveitits (EAU) test in rats are indicated. The rats were treated orally, once daily, for 14 days, either with

-♦- : Control (placebo, i.e. drug vehicle / water),

-■- : Compound of formula IIa (0.1 mg),

-▲-: Compound of formula I (15 mg), or

-⊠-: Compound of formula IIa (0.1 mg) + Compound of formula I (15 mg).

The weights in mg are indicated in mg/kg body weight/day. The means of scores of both eye lesions were determined as described in the examples within 20 days after immunization.

In **Figure 2**, results of the Experimental autoimmune uveitits (EAU) test in rats are indicated. The rats were treated orally, once daily, for 14 days, either with

-♦- : Control (placebo, i.e. drug vehicle / water),

-■- : Compound of formula IIa (0.1 mg),

-▲-: Compound of formula I (15 mg),

-⊠-: Compound of formula I (15 mg) + Compound of formula IIa (0.1 mg), 14 days, or

-*-: Compound of formula I (15 mg) + Compound of formula IIa (0.1 mg), 28 days.

Other parameters are as described for figure 1.

EXAMPLES

Example 1: EAU Test system

Experimental autoimmune uveitits (EAU)

The model of EAU used, is similar to that described previously by McAllister et al.(1986) *(McAllister CG, Vistica BP, Sekura R, Kuwabara T, Gery I. The effects of pertussis toxin on the induction and transfer of experimental autoimmune uveoretinitis. Clin Immunol Immunopathol 1986; 39: 329 – 336).* The animals (5 rats per group) are injected under ether anesthesia into the right foodpat with 50 µg of purified bovine retinal S-antigen and with 1 µg pertussis toxin (Difco) intra peritoneally on day 1. The antigen is diluted with

phosphate-buffered saline and mixed 1:1 (v/v) with Freund's complete adjuvant and Bacto M Tuberculosis H37 RA (Difco). The volume injected is 0.1 ml, containing 50 µl complete adjuvant and 1.14 mg of Mycobacterium tuberculosis. This procedure induces a fulimant disease in all animals which is observed earliest 9 – 10 days after immunisation. The eye lesions in untreated animals develop in allmost all animals to severity grade 4 (see section "Evaluation of EAU").

Treatment, dosages

The animals are treated by gavage with daily dosages of 15 mg/kg of a compound of formula I or 0.1 mg/kg of a compound of formula IIa alone; or with a combination of both compounds at the same dosage levels. The treatment is started 2 hours before immunisation and performed once daily on 14 consecutive days. Control animals are treated similarly with placebo / water alone (placebo: drug vehicle alone).

Evaluation of EAU

Starting on day 7 after immunisation the animals are examined with an ophtalmoscop (Heine, Beta 200) for inflammatory changes daily up to day 20. The extent of ocular inflammation is semi-quantitatively assessed with scores from 0 to 4 (for 1 eye).

0: normal;

1: iris hyperemia;

2: iris hyperemia with vasculare dilatation;

3: early fibrinous exudate in the anterior chamber and moderate iris cell infiltration; and

4: large fibrin clot in anterior chamber or fibrin plugging of the pupil and severe iris cell infiltration.

Results

Animals (LEWIS rats) are treated orally either with 0.1 mg/kg of a compound of formula IIa or 15 mg/kg/day of a compound of formula I are not distinctively diffferent from placebo controls in the course and intensity of the disease (see e.g. TABLE 1 and Figure 1).

In contrast, the administration of both compounds at the same dosage levels causes a remarkably delay in onset of the disease (6 days later than in controls) and the intensity of the inflammation is remarkably less. The highest mean score of treated animals is 4.4 on day 19 compared with 8.0 on day 11 in controls.

TABLE 1

Test group	Dosis	EAU POS	EAU 10	EAU 1st	SCORE MAX	
					SCORE	DAY
Controls	0.0	5/5	5/5	10.0 (0.0)	8.0 (0.0)	11
Cpd IIa	0.1	4/4*)	2/5	10.5 (0.6)	8.0 (0.0)	13
Cpd I	15	5/5	1/5	11.8 (1.3)	6.8 (1.3)	14
Cpd IIa + Cpd I	1.5 +15	4/5	0/5	16 (1.4)	4.4 (3.3)	19

*) one animal lost on day 11 due to traumatic gavage

In TABLE 1 under "EAU POS" and "EAU 10" the number of affected animals / number of animals per group until end of the study (EAU POS), and on day 10 (EAU 10), respectively. are indicated. The following abbreviations are used:

Cpd I: Compound of formula I

Cpd IIa: Compound of formula IIa

Controls: Placebo (drug vehicles / water)

Dosis: oral, in mg/kg/day

EAU POS: Number of EAU positive rats

EAU 10: Incidence of EAU on day 10

EAU 1st: Day of first signs of EAU (mean ± SD)

SCORE MAX: Maximum score (mean of both eye lesions ± SD)

The results from the EAU-test (used as an assay example) indicate that the combination of a suboptimal dosage of a compound of formula I plus a suboptimal dosage of a compound of formula IIa is significantly superior in activity against EAU, than the use of a suboptimal dosage of a compound of formula I, or of a suboptimal dosage of a compound of formula IIa, respectively, alone (Table 1 and Figure 1). That effect allows the use of a suboptimal dosage of a compound of formula I plus a suboptimal dosage of a compound of formula IIa.

Example 2:

Animals (6 rates per group) were treated as described in example 1 with the doses given in table 2. As depicted in table 2 and figure 2 the combination tretament shows superior results over the treatment with single compounds. From the animal treated on 14 days with

both compounds, the first clinical signs were observed in one animal on day 16. Complete suppression of symptoms was observed also during the 4-week treatment period. Symptoms appeared earliest in one animal on day 34, 6 days after the last treatment.

TABLE 2

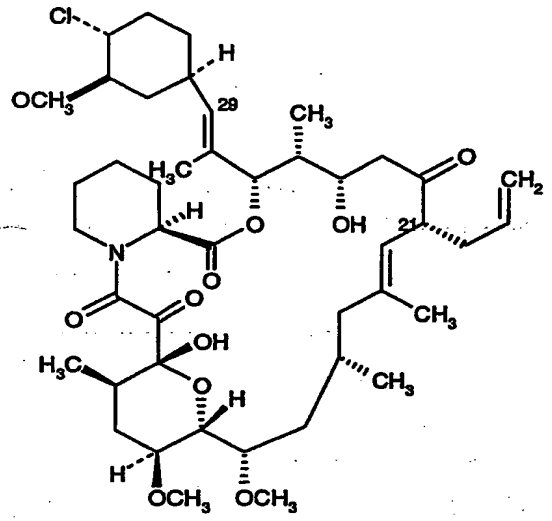
Test group	Dosis	EAU POS	EAU 10	EAU 1st	SCORE MAX	
					SCORE	DAY
Controls	-	6/6	6/6	9.3 (0.5)	8.0 (0.0)	12
Cpd IIa	0.1	6/6	0/6	11.2 (1.0)	8.0 (0.0)	14
Cpd I	15	6/6	2/6	11.5 (0.8)	6.0 (2.5)	14
Cpd I + Cpd IIa	15 + 0.1 (14x)	6/6	0/6	18.0 (1.1)	8.0 (0.0)	21
Cpd I + Cpd IIa	15 + 0.1 (28x)	6/6	0/6	34.8 (0.4)	7.2 (1.3)	37

The meanings are as in legend to table 1

The results from the EAU-test (used as an assay example) indicate that the development of the disease can be prevented when treatment is performed for 4 weeks starting at immunization with a combination of compounds I and IIa.

Patent Claims

1. A pharmaceutical composition comprising a compound of formula



I

and a 2-amino-1,3-propanediol beside one or more pharmaceutically acceptable excipient(s).

2. A package comprising a compound of formula I as defined in claim 1 in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s) and comprising instructions for simultaneous or sequential administration of a 2-amino-1,3-propanediol.

3. A package comprising a 2-amino-1,3-propanediol in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s) and comprising instructions for simultaneous or sequential administration of a compound of formula I as defined in claim 1.

4. A pharmaceutical kit, comprising a compound of formula I as defined in claim 1 in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s) and a 2-amino-1,3-propanediol in the form of a pharmaceutical composition beside one or more pharmaceutically acceptable excipient(s) in the same package.

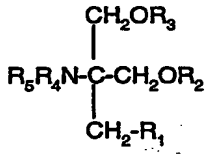
5. Use of a compound of formula I as defined in claim 1 in combination with a pharmaceutically active 2-amino-1,3-propanediol as a pharmaceutical.

6. Use of a combination of a compound of formula I as defined in claim 1 and a 2-amino-1,3-propanediol in the preparation of a medicament for the treatment of diseases, wherein a compound of formula I and a 2-amino-1,3,-propanediol are pharmaceutically active.

7. A method of improving the pharmaceutical activity of a compound of formula I and of a pharmaceutically acceptable 2-amino-1,3-propanediol which method comprises co-administrating a compound of formula I and a 2-amino-1,3-propanediol to a subject in need of a treatment with a compound of formula I and/or with a 2-amino-1,3-propanediol.

8. A method of treatment of diseases, wherein a compound of formula I as defined in claim 1 and a 2-amino-1,3-propanediol are pharmaceutically active, comprising administering to a subject in need of such treatment an effective amount of a compound of formula I as defined in claim 1 and a 2-amino-1,3-propanediol.

9. A method, a pharmaceutical composition, a pharmaceutical kit, a package or the use as claimed in any one of the preceding claims, wherein the 2-amino-1,3-propanediol is a compound of formula



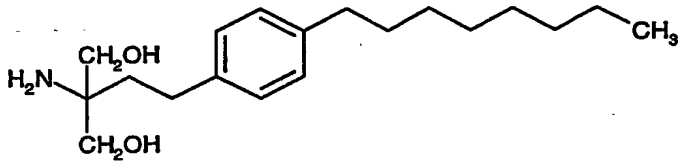
II

wherein

R_1 is an optionally substituted straight- or branched (C_{12-22})carbon chain, and,

independently of each other, R_2, R_3, R_4 and R_5 are H or lower alky.

10. A method, a pharmaceutical composition, a pharmaceutical kit, a package or the use as claimed in claim 9, wherein a compound of formula II is of formula



IIa

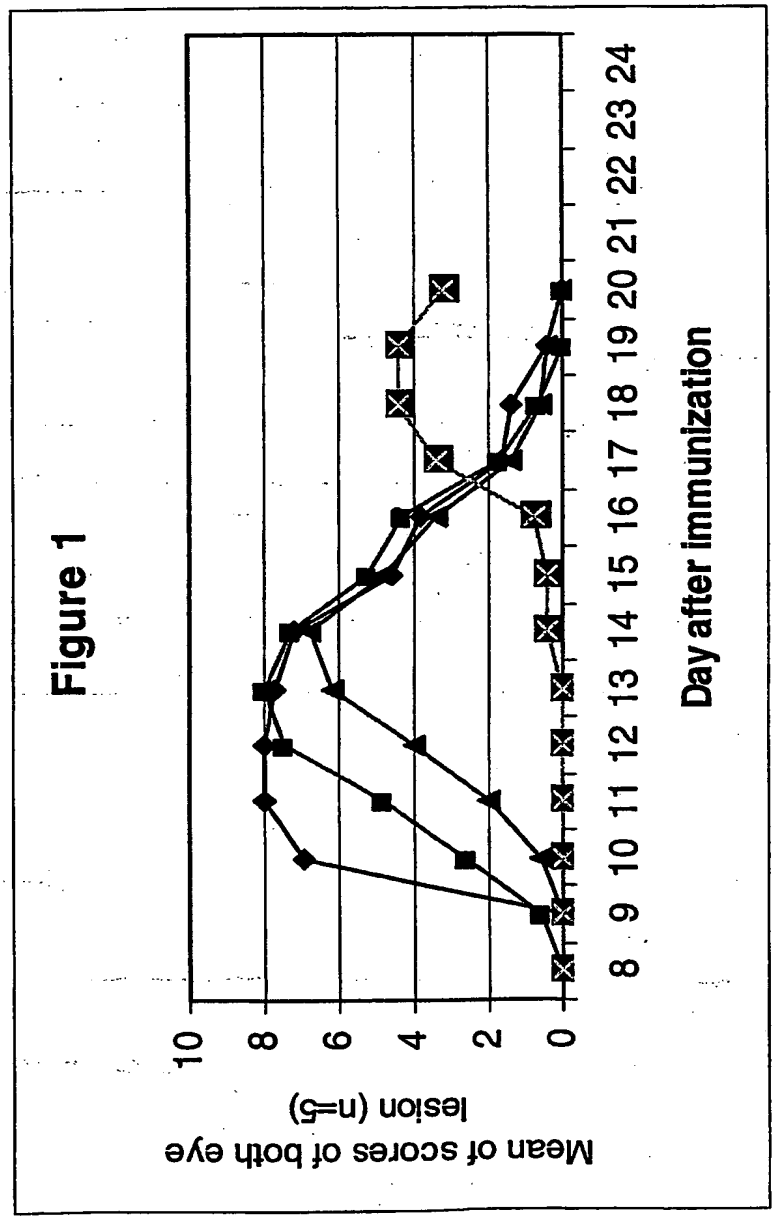
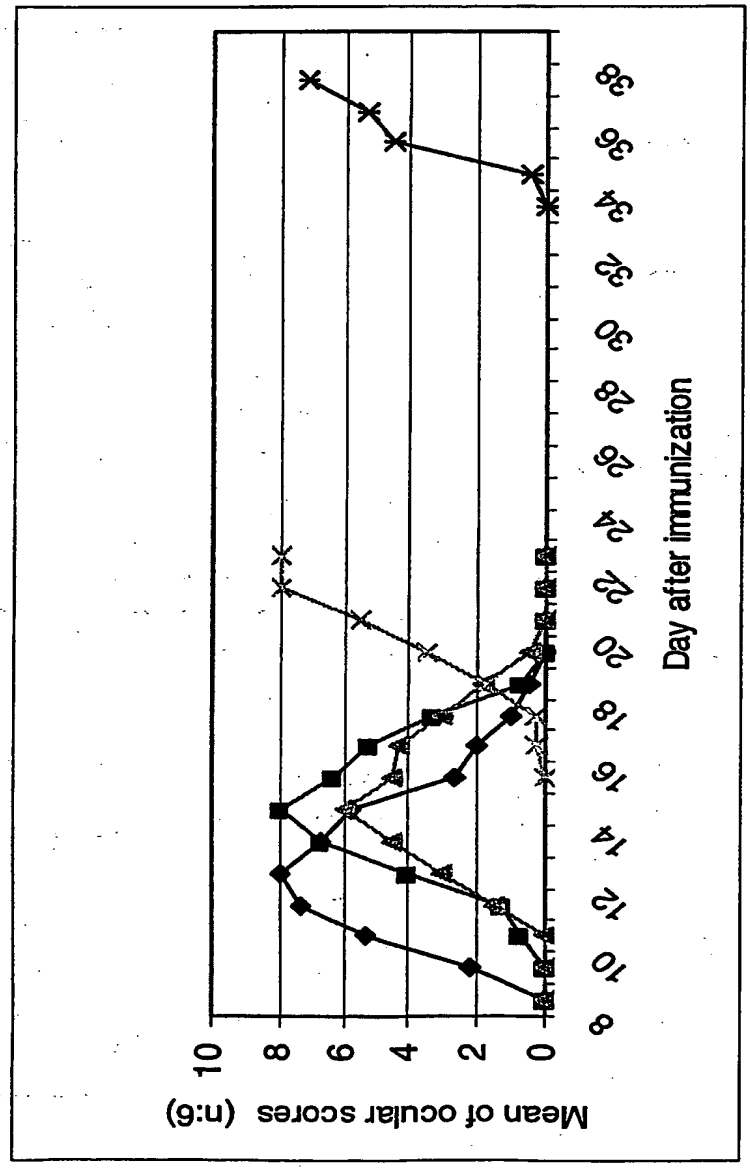


Figure 1
Mean of scores of both eye lesion (n=5)
0
2
4
6
8
10
Day after immunization
8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24

Figure 2


Mean of ocular scores (n:6)
0
2
4
6
8
10
Day after immunization
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38

INTERNATIONAL SEARCH REPORT

Internati Application No
PCT/EP 02/11799

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/436 A61K31/133 A61K31/135

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, MEDLINE, EMBASE, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 427 680 A (SANDOZ LTD ;SANDOZ AG (DE); SANDOZ AG (AT)) 15 May 1991 (1991-05-15) cited in the application the whole document	1-10
A	EP 0 627 406 A (YOSHITOMI PHARMACEUTICAL) 7 December 1994 (1994-12-07) cited in the application the whole document	1-10
A	EP 0 778 263 A (YOSHITOMI PHARMACEUTICAL) 11 June 1997 (1997-06-11) cited in the application the whole document	1-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 January 2003	31/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Siatou, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ional application No.
PCT/EP 02/11799

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8 and 9-10 (in part) are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 02/11799

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 002 792 A (YOSHITOMI PHARMACEUTICAL) 24 May 2000 (2000-05-24) cited in the application the whole document	1-10
A	GB 2 252 041 A (FUJISAWA PHARMACEUTICAL CO) 29 July 1992 (1992-07-29) the whole document	1-10

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 02/11799

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0427680 A	15-05-1991	AT 126803 T	15-09-1995
		AU 640963 B2	09-09-1993
		AU 6584390 A	23-05-1991
		CA 2029694 A1	10-05-1991
		DE 69021833 D1	28-09-1995
		DE 69021833 T2	21-03-1996
		DK 427680 T3	18-12-1995
		EP 0427680 A1	15-05-1991
		ES 2077663 T3	01-12-1995
		GR 3017858 T3	31-01-1996
		HK 30096 A	23-02-1996
		HU 210900 B3	28-09-1995
		IE 904023 A1	22-05-1991
		IL 96268 A	23-07-1996
		JP 2750302 B2	13-05-1998
		JP 3223291 A	02-10-1991
		KR 166074 B1	15-01-1999
		LV 11621 A	20-12-1996
		LV 11621 B	20-04-1997
		NZ 235991 A	26-05-1993
		US 5912238 A	15-06-1999
		US 5352671 A	04-10-1994
		ZA 9009024 A	29-07-1992
EP 0627406 A	07-12-1994	DE 69321823 D1	03-12-1998
		DE 69321823 T2	02-06-1999
		DK 627406 T3	12-07-1999
		EP 0627406 A1	07-12-1994
		HK 1013281 A1	02-06-2000
		US 5604229 A	18-02-1997
		AT 172711 T	15-11-1998
		CA 2126337 A1	28-04-1994
		ES 2126658 T3	01-04-1999
		WO 9408943 A1	28-04-1994
		JP 2579602 B2	05-02-1997
		KR 155015 B1	01-12-1998
		US 5719176 A	17-02-1998
		US 5952316 A	14-09-1999
EP 0778263 A	11-06-1997	AT 211726 T	15-01-2002
		DE 69524962 D1	14-02-2002
		DE 69524962 T2	31-10-2002
		DK 778263 T3	22-04-2002
		EP 0778263 A1	11-06-1997
		US 6187821 B1	13-02-2001
		US 6372800 B1	16-04-2002
		US 5948820 A	07-09-1999
		CA 2198383 A1	29-02-1996
		ES 2171191 T3	01-09-2002
		WO 9606068 A1	29-02-1996
		PT 778263 T	28-06-2002
EP 1002792 A	24-05-2000	AU 735853 B2	19-07-2001
		AU 6523098 A	30-10-1998
		BR 9808481 A	23-05-2000
		EP 1002792 A1	24-05-2000
		NZ 500713 A	28-07-2000
		US 6214873 B1	10-04-2001

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/11799

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1002792 A		CN 1259117 T	05-07-2000
		WO 9845249 A1	15-10-1998
GB 2252041 A	29-07-1992	NONE	